IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Raymond Nadeson *et al.*	Confirmation No.:	9722
Serial No.:	10/574,438	Group Art Unit:	1619
Filed:	June 25, 2007	Examiner:	RAO, Savitha M.

FOR: **METHODS AND COMPOSITIONS**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PROF. DAVID ADAMS UNDER 37 C.F.R. § 1.132

Commissioner for Patents,

I, Prof. David Adams, pursuant to 37 C.F.R. § 1.132, hereby declare:

1. I am the Director of Health Innovations Research Institute at RMIT University, Melbourne Australia. I hold a Bachelor of Science (Hons I) and a PhD (Physiology) from the University of NSW. I am President of the Australian Physiological Society and hold an Australian Research Council (ARC) Professorial Fellowship (2010-2014).

2. I have expertise in neuroscience and membrane physiology using electrophysiological, molecular biological and fluorescence imaging techniques to study membrane receptors and ionic channels and calcium signaling. Particular expertise is in the modulation of receptor and ion channel function and the ionic mechanisms underlying neuronal excitability in sensory neurons using patch clamp recording techniques with a focus on those targets involved in analgesia. I have published widely in the field with over 145 refereed journal articles, 15 book chapters and >160 abstracts and my work has

been cited in over 5000 publications. My Curriculum Vitae is attached as **Exhibit A,** which evidences my area of academic credentials.

3. I have specialist expertise on the family of potassium ion channels and NMDA receptors, as evidenced by my recent publications on these targets (Schuetz *et al* (2008); Yasuda *et al* (2008); Ekberg *et al*. (2007) and Kloda *et al*. (2008)) and I am knowledgeable on the mechanism of action, pharmacokinetics and the analgesic effects of openers of K_V7 ion channels such as flupirtine and antagonists of N-methyl-D-aspartate (NMDA) receptors such as ketamine.

4. I have been briefed by patent counsel in respect of U.S. Patent Application No. 10/574,438, assigned to Relevare Australia Pty Ltd., and the Official Action issued from by the U.S. Patent and Trademark Office on September 13, 2011.

5. I have reviewed the Office Action and the references cited by the Examiner.

6. I have reviewed claims 52-59 submitted concurrently with the Declaration and understand the subject matter presently claimed.

7. I understand that the Examiner asserts that previous claims 43-45, 48-49, and 51 are allegedly obvious over Nickel *et al.* (U.S. Patent No. 5,521,178) in view of Williams *et al.* (U.S. Application No. 2004/0076648), Chizh *et al.* (U.S. Application No. 2004/0092531), and Schwartz *et al.* (U.S. Patent No. 5,721,258) and that the Examiner further asserts that previous claim 46 is allegedly obvious over Nickel *et al.* (U.S. Patent No. 5,521,178) in view of Williams *et al.* (U.S. Application No. 2004/0076648), Chizh *et al.* (U.S. Application No. 2004/0092531), Schwartz *et al.* (U.S. Patent No. 5,721,258), and Perovic *et al.* (*Neurodegeneration.* 4:369-374, 1995).

8. In particular, I understand that the Examiner alleges that at the time the subject application was filed, a person of ordinary skill in the art would have recognized flupirtine as an NMDA receptor antagonist.

9. I further understand that the Examiner alleges that a person of ordinary skill in the art would have been motivated to substitute flupirtine for ketamine, an NMDA receptor antagonist, on the basis that flupirtine is an alleged NMDA receptor antagonist.

10. For the reasons outlined below, despite the allegation that Williams *et al.* and certain other references teach that flupirtine was an NMDA receptor antagonist, at the time the subject application was filed, a person of ordinary skill in the art was in possession of a substantial body of evidence that flupirtine was not an NMDA receptor antagonist. In addition, post-filing data provides unequivocal evidence that flupirtine is not an NMDA receptor antagonist. Accordingly, in view of the knowledge in the art at the time of filing and the rationale provided by the Examiner in the Office Action issued September 13, 2011, it is my reasoned opinion that a person of ordinary skill in the art would not have viewed flupirtine and ketamine as equivalents; and would not have reasonably expected to successfully substitute flupirtine for ketamine in combination with an opioid, in a method for inducing an analgesic response in a mammal having neuropathic pain, as claimed.

11. At the time the application was filed, the term "antagonist" referred to molecules that bind to certain proteins at a specific site on that protein in order to suppress or inhibit the activity of that protein (*see* Kimball Nill, *Glossary of Biotechnology Terms*. 3rd edition, CRC Press, FL, 2002, page 13). Accordingly, the term "NMDA receptor antagonist" would have been understood to refer to a molecule that binds to an NMDA receptor at a specific site on the NMDA receptor in order to suppress or inhibit the activity of the NMDA receptor.

12. A molecule that indirectly suppresses or inhibits the activity of an NMDA receptor without binding to the NMDA receptor would not have been considered an NMDA receptor antagonist. As stated above, the art-accepted definition of a NMDA receptor antagonist requires direct binding of the molecule to the NMDA receptor, not an indirect effect of a molecule on an NMDA receptor. Accordingly, because it was known at the time of filing that flupirtine does not bind the NMDA receptor, flupirtine was not considered an NMDA receptor antagonist.

13. Flupirtine was not considered an NMDA receptor antagonist because flupirtine had been empirically shown to have no detectable binding affinity for the known binding sites of the NMDA receptor. Osborne *et al.* (*Invest. Opthalmol. Vis. Sci.* 37: 274-280, 1996) stated that binding studies between flupirtine and NMDA receptors failed to indentify any detectable affinity of flupirtine to the known binding sites of the NMDA receptor.

14. Flupirtine was not considered an NMDA receptor antagonist because empirical studies had shown that flupirtine does not directly bind the NMDA receptor, even at extremely high and physiologically irrelevant concentrations (1000 μM). Jakob and Krieglstein (*British Journal of Pharmacology*. 122:1333-1338, 1997) concluded that 1000 μM flupirtine did not directly affect NMDA-induced currents in rat cultured hippocampal neurons by use of the whole-cell configuration of the patch-clamp technique, which is the gold-standard in characterizing ion channel physiology (*Id.* at 1333, 1336). Thus, prior to the time of filing, Jakob and Krieglstein had empirically shown that flupirtine is not an NMDA receptor antagonist because it does not bind the NMDA receptor.

15. Flupirtine was not considered an NMDA receptor antagonist because at best, empirical studies had shown that flupirtine only indirectly affects NMDA receptor currents – an affect that was only measurable at physiologically-irrelevant or clinically-irrelevant concentrations. Kornhuber *et al.* (*Journal of Neural Transmission*. 106:857-867, 1999) carefully analyzed the mechanism of action of flupirtine using direct whole cell patch clamp studies and found no direct binding to the NMDA receptor at physiologically-relevant concentrations (*Id.* at 858, 862-863). Kornhuber *et al.* merely stated that flupirtine may indirectly affect NMDA receptors, this indirect effect being a result of the Mg^{2+} block of the NMDA receptor remaining in force due to stabilization of the resting membrane potential through direct interaction with non-NMDA receptors (*Id.* at 864).

16. A person of ordinary skill in the art would not have classified flupirtine as an NMDA receptor antagonist and would not have substituted flupirtine for existing

NMDA receptor antagonists because flupirtine had only been shown to indirectly affect NMDA receptor current at exceedingly high and clinically-irrelevant concentrations (Note that at such high concentrations flupirtine would likely also affect other currents, as would many other agents). Table 1 highlights the potency of NMDA receptor antagonists such as ketamine in reducing NMDA-induced currents in hippocampal neurons compared to flupirtine.

Table 1: NMDA Receptor Antagonist Activity

Compound	EC_{50} (μM)	Comment
MK-801*	0.12	Strong
Ketamine*	0.43	Medium-to-strong
Memantine*	1.04	Considered weak
Flupirtine#	182	1500x weaker than MK-801; 423x weaker than Ketamine; 175x weaker than Memantine

*Parsons *et al. Eur. J. Neurosc.* 8(3), 446-54, 1996; # Kornhuber *et al. Journal of Neural Transmission*. 106:857-867, 1999

Table 1 shows that even assuming a so-called "functional" NMDA receptor antagonist activity of flupirtine, the levels of flupirtine required to achieve this activity were known to be too high to be physiologically or clinically relevant. Accordingly, because the art prior to the time of filing had empirically established that flupirtine only indirectly affects NMDA receptor currents at concentrations at that are least 423 times greater than ketamine, that is, at clinically-irrelevant concentrations, a person of ordinary skill in the art would have had no reasonable technical basis to substitute flupirtine for ketamine in a method for inducing an analgesic response in a mammal having neuropathic pain.

17. A person of ordinary skill in the art would not have classified flupirtine as an NMDA receptor antagonist, because at the time the subject application was filed, flupirtine was instead identified as a potassium channel agonist. Jakob and Krieglstein, using whole-cell patch clamp techniques in rat hippocampal neurons, found that the only mechanism for flupirtine relevant in a therapeutic concentration range (0.6 μM) was the activation of G-protein-regulated inwardly rectifying K^+ channels (GIRK) (Jakob and Krieglstein at 1334-1335). Kornhuber *et al.* also used whole-cell patch clamp studies and binding assays to determine that flupirtine does not directly activate NMDA receptors (Kornhuber *et al.* at 859-860). Kornhuber *et al.* concluded that flupirtine activated GIRK

channels at low, clinically relevant, concentrations (< 5μM) consistent with the findings of Jakob and Krieglstein (*Id.* at 864-865). Thus, at the time the subject application was filed, specific research into the mechanism of action of flupirtine demonstrated that it activates an inwardly-rectifying potassium current in cultured hippocampal neurons and also demonstrated the absence of a direct effect of flupirtine (at physiologically- or clinically-relevant concentrations) on NMDA receptors in these neurons. Accordingly, a person of ordinary skill in the art would have had no reasonable technical basis to substitute flupirtine for ketamine in a method for inducing an analgesic response in a mammal having neuropathic pain.

18. At the time the subject application was filed, a person of ordinary skill in the art would have concluded that flupirtine was a KCNQ potassium channel agonist and not an NMDA antagonist.

A. Wang *et al.* (*Science.* 282: 1890-1893, 1998) first identified the KCNQ2 and KCNQ3 channels, and later other members of this family, as molecular substrates for the M currents. M currents are a primary mechanism by which neurotransmitters and neuromodulators control neuronal excitability (reviewed in Micelli *et al. Curr Opin Pharmacol* 8(1): 65-74, 2008).

B. Flupirtine was also found to shift the activation curves toward negative voltages in KCNQ2/3 channels (Wu *et al.*, *J. Med. Chem. 46,* 3197-3200, 2003).

C. Passmore *et al.* (*J. Neurosci.* 23(18): 7227-7236, 2003) provided evidence supporting a key role of KCNQ-channels in controlling the excitability of nociceptors and thereby representing a novel analgesic target. Passmore *et al.* showed the presence of KCNQ channels in nociceptive sensory systems and identified M currents [termed $I_{K(M)}$] in cultured dorsal root ganglia neurons were inhibited by M-channel blockers and enhanced by retigabine.

D. Gribkoff (*Expert Opin. Ther. Targets.* 7(6): 737-48, 2003) reviewed the state of the art in KCNQ channels and pain pathway research and linked research between M currents, KCNQ channels, pain pathways and channel openers such as retigabine and flupirtine.

Collectively, these reports and others unambiguously established that flupirtine was a KCNQ channel agonist because it targets the same family and subtypes of KCNQ channels, previously referred to as GIRK channels.

19. Contemporaneous and post-filing data further confirm that flupirtine is a KCNQ channel agonist and not an NMDA receptor antagonist.

A. Martire *et al.* (*J. Neurosci.* 24(3): 592-7, 2004) performed electrophysiological studies in KCNQ2-transfected Chinese hamster ovary cells and revealed that flupirtine caused a hyperpolarizing shift in the voltage dependent activation of KCNQ2 channels.

B. Munro and Dalby-Brown (*J. Med. Chem.* 50: 2576-2582, 2007) attribute the pharmacological effect of flupirtine in analgesia to its K_V7 channel agonist activity. "A particular facet of flupirtine-mediated analgesia in humans is that it is obtained at doses associated with plasma concentrations in the low micromolar range, which suggests that K_V7 channel opening is the likeliest pharmacological mechanism to account for this action." *Id.* at 2580.

C. Brown and Passmore (*British Journal of Pharmacology*. 156: 1185-1195, 2009) disclose that flupirtine enhances neural K_V7/M-channel activity, principally through a hyperpolarizing shift in their voltage gating. *Id.* at 1185. Brown and Passmore further conclude that flupirtine can reduce neural excitability and can inhibit nociceptive stimulation and transmission. *Id.* Flupirtine's use as a central analgesic is also disclosed. *Id.*

D. Wulff *et al.* (*Nat. Rev. Drug Discov.* 8(12): 982-1001, 2009) state that "[t]he clear role of K_V7 channels in controlling neuronal excitability, combined with expression of $K_V7.x$ channels in sensory and central neurons involved in nociceptive signaling, has further prompted the exploration of $K_V7.2–7.5$ activators for the treatment of pain. Wulff *et al.* further state that flupirtine produces analgesic activity in rat models of neuropathic pain." *Id.* at 993.

Accordingly, contemporaneous and post-filing studies have further confirmed that flupirtine was a K_V7 channel opener and not a NMDA antagonist.

20. In view of the foregoing reasons, it is my reasoned opinion that a person of ordinary skill in the art would not have considered flupirtine an NMDA receptor antagonist at the time the subject application was filed. Likewise, such a person would not have considered flupirtine and ketamine as functional equivalents for antagonizing an NMDA receptor at clinically-relevant concentrations. Accordingly, it would not have been technically reasonable for a person of ordinary skill in the art to clinically substitute flupirtine for ketamine on the basis that both are capable of antagonizing an NMDA receptor. Thus, in view of the knowledge in the art at the time of filing and the rationale provided by the Examiner in the Office Action issued September 13, 2011, it is my reasoned opinion that a person of ordinary skill in the art would have had no reasonable technical basis to derive a method for inducing an analgesic response in a mammal having neuropathic pain, comprising administering to the mammal a composition comprising flupirtine and an opioid, as claimed.

21. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful, false statements, and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

David Adams, Ph.D.

24 November 2011
Date